Reconstruction of integrated maps for drug efficacy assessment

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Background.
Analysis of biological network and signaling pathways is widely used for investigation of
cell processes, mechanisms of disease, drug development and analysis of drug repurposing perspectives.
Different scientific groups develop similar conceptions of biological networks and
pathways that represent processes in norm, but conceptions of disease-specific
pathways and drug mechanism of action pathways can differ significantly among
researchers. Previously, we’ve developed the conception of disease-specific pathway
maps that show affected normal processes in pathology and some steps that newer
have been detected in norm. The disease maps show enhanced and weakened
interactions or reactions under pathological conditions resulting from mutations or
abberant gene expression.
Another conceptions was compilation of disease-specific pathways with drug,
xenobiotic or another enviromental factor action in one maphat represent both
disease-specificity and drug-induced perturbations.

Research objective.
The aim of research was to elucidate mechanisms of acquired or hereditary drug
resistance for small group of patients suffering from breast cancer with triple negative
phenotype (TNBC).

Materials and methods.
Group of 10 patients suffered from TNBC has been enrolled in study. All patients have
got similar antitumor therapy. Whole exome sequencing and whole transcriptome
analysis were performed for the genomic DNA and RNA obtained from tumor samples.
DAVID and MetaCore have been used for functional and integrated analysis.
Reconstruction of integrated maps of tumor processes has been performed in Cytoscape
APP.

Results.
Whole exome sequence showed high heterogeneity of tumor samples. Several
hereditary risk factors (mutations in TP 53/ Li-Fraumeni syndrome, mutation in MSH6/
Lynch syndrome) and damaging mutations in well-known driver genes were detected in
patient samples.
Analysis of tumor gene expression data allowed to reveal the concordance of patient
data with different subtypes of Lehmann's classification of TNBC. Pathway analysis by
MetaCore and David wasn’t capable to explain tumor drug resistance in patients. So for
the aims of this project we’ve combined conceptions of disease-specific and drug
mechanism of action maps and reconstructed integrated models using Cytoscape.
Compilation of different types of data in these maps allowed to clearly define
differences between Lehmann’s subtype patients and explain possible drug resistance
mechanisms in each subtype.

Conclusion.
Compilation of disease-specific pathways and mechanisms of drug action with genetic,
farmacogenomic and expression data allows to build comprehensive models that reflect
processes of tumor progression and in some cases explain the drug resistance.